Dabigatran associated with increased risk of acute coronary events

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The anticoagulant dabigatran is associated with an increased risk of myocardial infarction (heart attack) or acute coronary syndrome in a broad spectrum of patients when tested against some other medicines, according to a study published Online First by the *Archives of Internal Medicine*.

"Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran," the study concludes.

Dabigatran etexilate was approved by the European Medicines Agency in 2008 for prevention of venous thromboembolism (VTE) in adults who have undergone total hip or knee replacement and by the U.S. Food and Drug Administration in 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), the authors write as background in the study. An original trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran compared to warfarin in patients with atrial fibrillation.

Ken Uchino, M.D., and Adrian V. Hernandez, M.D., Ph.D., of the Cleveland Clinic in Ohio, searched the medical literature for randomized controlled trials of dabigatran that reported on MI or acute coronary syndrome (ACS) as secondary outcomes. Seven trials were selected, involving 30,514 participants, for their meta-analysis.

The trials they included were: two studies of stroke prophylaxis in atrial fibrillation, one in acute venous thromboembolism, one in ACS and three trials or short-term prophylaxis of deep venous thrombosis in joint replacement. The control groups included administration of warfarin, enoxaparin or placebo.

"Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group" (dabigatran, 237 events of 20,000 [1.19 percent] vs. control, 83 events of 10,514 [0.79 percent]), the researchers write.

They note the risk of MI or ACS was similar when using revised results of a previous trial and after the exclusion of short-term trials. The authors comment that they used several meta-analytic methods and association measures and the results were consistent.

"Although the relative risk increase was 33 percent, the absolute risk increase was very small, at 0.27 percent," they write.

They suggest that while dabigatran might not directly increase the risk of MI, it may lack the beneficial effects that warfarin and aspirin have in MI prevention. They note they do not know the pharmacologic mechanism that may result in dabigatran increasing the risk of MI or ACS.

"The overall benefit and risk balance of dabigatran use appears to be favorable in patients with AF because of reduction in ischemic stroke. However, the cardiac risk of dabigatran should be investigated further, especially if it is used in populations at high risk of MI or ACS," the authors conclude.

In an accompanying invited commentary, Jeremy M. Jacobs, M.B.B.S., and Jochanan Stessman, M.D., of the Hadassah-Hebrew University Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel, write: "The robust finding that dabigatran is associated with increased rates of MI is alarming and emphasizes the need for continued critical appraisal of new drugs after phase 3 trials."

"Uchino and Hernandez have drawn our attention to the potential safety issue concerning dabigatran and the risk of MI, extracting data from the small number of available RCTs (randomized controlled trials) amidst a plethora of recent literature. A far wider issue of perhaps deeper concern is the enthusiasm - nearly to the level of euphoria - to embrace the new, which must be restrained by the

old aphorism: primum non nocere. Only a balanced view of all high-quality data for dabigatran can permit such an assessment necessary to guide clinical decisions," they conclude.

More information:
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